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Evaluation Report ERC2011-07

Paecilomyces fumosoroseus strain FE 9901

(publié aussi en français)

12 October 2011

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-1238 (print)
1911-8082 (online)

Catalogue number: H113-26/2011-7E (print version)
H113-26/2011-7E-PDF (PDF version)

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Overview

Registration Decision for *Paecilomyces fumosoroseus* strain FE 9901

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of NoFly Technical and NoFly WP, containing the technical grade active ingredient *Paecilomyces fumosoroseus* strain FE 9901, to control whiteflies in greenhouse crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of NoFly Technical and NoFly WP.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA section of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

What Is *Paecilomyces fumosoroseus* strain FE 9901?

Paecilomyces fumosoroseus strain FE 9901 is a fungus that can cause a fatal disease in many insects. Formulated into the end-use product NoFly WP and applied as a foliar spray, it can provide control of whiteflies, which are serious pests of a wide variety of greenhouse crops in Canada.

Health Considerations

Can Approved Uses of *Paecilomyces fumosoroseus* strain FE 9901 Affect Human Health?

***Paecilomyces fumosoroseus* strain FE 9901 is unlikely to affect your health when NoFly WP is used according to the label directions.**

People could be exposed to *P. fumosoroseus* strain FE 9901 when handling and applying NoFly WP. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (e.g. production of toxic byproducts);
- reports of any adverse incidents;
- its potential to cause disease or toxicity as determined in toxicological studies; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

Toxicological studies in laboratory animals describe potential health effects from large doses in order to identify any potential pathogenicity, infectivity and toxicity concerns. When spores of *P. fumosoroseus* strain FE 9901 were tested on laboratory animals, there were no signs that it caused any significant toxicity or disease. Furthermore, *P. fumosoroseus* strain FE 9901 does not grow at temperatures above 35°C and no adverse effects to *P. fumosoroseus* were reported in published scientific literature.

Residues in Water and Food

Dietary risks from water and food are not of concern

The *Food and Drugs Act* (*FDA*) prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *FDA* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value determines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

As there are no direct applications to food, there is no concern for risks posed by dietary exposure of the general population, including infants and children, or animals. Consequently, the establishment of an MRL is not required for *P. fumosoroseus* strain FE 9901. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent.

Occupational Risks From Handling NoFly WP

Occupational risks are not of concern when NoFly WP is used according to label directions, which include protective measures

Growers handling NoFly WP can come into direct contact with *P. fumosoroseus* strain FE 9901 on the skin, in the eyes or by inhalation. For this reason, the product labels specify that growers exposed to these end-use products must wear waterproof gloves, long-sleeved shirts, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks. Eye goggles are not required as the eye irritation studies submitted indicated minimal eye irritation potential.

For the bystander, exposure is expected to be much less than that of handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When NoFly WP Is Introduced Into the Environment?

Environmental risks are not of concern

Following application, *Paecilomyces fumosoroseus* strain FE 9901 is likely able to survive in the environment under favourable environmental conditions (i.e. temperature, humidity) but that over time populations of *P. fumosoroseus* strain FE 9901 are expected to return to natural background levels.

The effects of *P. fumosoroseus* strain FE 9901 on beneficial and/or environmentally-important insects were examined. Studies showed that *P. fumosoroseus* strain FE 9901 was toxic or infectious to some beneficial insects, however, no adverse effects to wasps were found. The end-use product label will advise users that NoFly WP may be harmful to pollinators, including bees, and to some beneficial insects, and will alert users to avoid applying NoFly WP directly to bees while they are foraging. This is a precautionary measure aimed at minimizing exposure of bees even though there are no reports indicating that *P. fumosoroseus* is pathogenic or toxic to bee species.

Although avian pulmonary/inhalation/injection, wild mammal, fish, aquatic insect, earthworms, microorganisms, and plant testing were not conducted, adequate information was available to determine that significant adverse effects to these non-target organisms are not expected. There are no published reports of disease associated with *P. fumosoroseus* strain FE 9901 in birds, wild mammals, fish, aquatic insects, earthworms, microorganisms, and plants. Also, minimal exposure to non-target organisms is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses.

Value Considerations

What Is the Value of NoFly WP?

Applied as a foliar spray, NoFly WP can provide control of whiteflies on greenhouse crops and is compatible with the use of *Encarsia* species as biological control agents.

The value of NoFly WP is that it provides an effective alternative for control of whiteflies in the greenhouse environment. Whiteflies are serious pests of a wide variety of greenhouse crops in Canada and certain species have been known to develop resistance to chemical insecticides. NoFly WP provides a new, non-chemical, mode of action and has been shown to be compatible with the use of *Encarsia* species, parasitoids that are commonly used as biological control agents for whiteflies in greenhouses.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of NoFly WP to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

As with all microbial pest control products, there are concerns with users developing allergic reactions through repeated high exposures to *P. fumosoroseus* strain FE 9901. Therefore, anyone handling NoFly WP must wear waterproof gloves, long-sleeved shirts, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks. Eye goggles are not required as the eye irritation studies submitted indicated minimal eye irritation potential. An additional risk reduction measure is a 4-hour restricted entry interval immediately following product application. All early-entry workers to treated sites will be required to wear personal protective equipment, including a NIOSH-approved respirator until spray mists have settled.

Environment

As a general precaution, the label prohibits the direct application of the product to aquatic habitats (such as lakes, streams and ponds). The label also directs growers to not allow effluent or run-off from greenhouses containing this product to enter lakes, streams, ponds or other waters and to avoid contaminating surface water by disposal of equipment wash waters.

The product label further advises users that NoFly WP may be harmful to pollinators (including bees) and to some beneficial insects that may be used in greenhouse integrated pest management programs. A statement will also instruct users to avoid direct applications to bees while they are foraging.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Human Health

Confirmatory analysis data for potency and microbial contamination are required from five full-scale production lots of NoFly WP and NoFly Technical produced at the proposed site of manufacture. The data must be provided to the PMRA within three years of the original registration decision for these products.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

[3] As per subsection 28(1) of the *Pest Control Products Act*.

Science Evaluation

Paecilomyces fumosoroseus strain FE 9901

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active microorganism	Paecilomyces fumosoroseus strain FE 9901
Function	control of whitefly by infecting and killing eggs, larvae and adults
Binomial name	Paecilomyces fumosoroseus strain FE 9901
Taxonomic designation[1]	
Kingdom	Fungi
Sub-kingdom	Dikarya
Phylum	Ascomycota
Sub-phylum	Pezizomycotina
Class	Sordariomycetes
Sub-class	Hypocreomycetidae
Order	Hypocreales
Genus	Paecilomyces
Species	fumosoroseus
Strain	FE 9901
Patent Status information	No patents are held by the applicant in Canada.
Nominal purity of active	8.1×10^9 colony forming units (CFU)/mL
Identity of relevant impurities of toxicological, environmental and/or significance.	The technical grade active ingredient (TGAI) does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy Track 1 substances. The product must meet microbiological contaminants release standards. Cultures of *P. fumosoroseus* strain FE 9901 have been shown to produce beauverolides M and I and extracts of these cultures have been shown to be cytotoxic against HL60 cells (human lymphoblast like), human lung cancer cells and Madin Darby canine kidney cells.

[1] http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id=114497

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—NoFly Technical

Physical state	powder
Guarantee	8.1×10^9 CFU/mL (nominal)
Colour	lilac (near Pantone 435M)
Odour	yeast-like
Particle size	99% < 100 µm
Density	0.6 to 0.7 g/cc

End-Use Product—NoFly WP

Physical state	powder
Guarantee	2.0×10^9 CFU/mL (nominal)
Colour	lilac (Pantone 435M/662C)
Odour	Yeast-like
Density	0.65 to 0.75 g/cc

1.3 Directions for Use

For use in controlling whiteflies on all greenhouse ornamental crops.

NoFly WP contains live blastospores of the naturally occurring fungus *Paecilomyces fumosoroseus* strain FE 9901 and food grade inert ingredients. The spores are alive and may be harmed by storage at high temperatures or contact with water for more than 24 hours.

NoFly WP can generally be applied using conventional spraying equipment. Use of manual sprayers is highly recommended; with a minimum working pressure of four psi.

NoFly WP works best in a pest management program designed to keep insect populations below levels which damage crops. Typically, it takes three to seven days for an infected insect to die and seven to ten days after the first spray to see a reduction in an insect population. Application rates, spray frequency, spray coverage and insect numbers affect the speed at which insect populations are reduced. Frequent scouting for insects in crops is recommended. NoFly WP is most effective when used at the first appearance of insects in the crop, before high insect populations develop.

Crops	Application Rate	Application Timing
Greenhouse ornamentals	3 g/L up to a maximum of 2000 L/ha	At any stage of the crop. Applications must begin at the first sign of pest presence.

Application Instructions:

- Begin applications at the first sign of pest presence. Reapply at 15-day intervals, or shorter (5-8 days) in the case of heavy infestations, up to a maximum of three applications.
- Apply sufficient spray volume for thorough coverage of the crop, depending on the size of the plants, up to a maximum of 2000 L/ha. Ensure spray coverage includes the undersides of the leaves.
- Dissolve the content of bags in appropriate volume of water and mix with a stirring device to get a blue homogeneous suspension. Apply immediately using conventional spraying equipment. A minimum pressure of four psi is recommended for the applications.
- Applications should be conducted during low solar radiation (late afternoon or evening) when there is high relative humidity inside the greenhouse and the temperature is below 30°C.
- NoFly WP is compatible with the use of *Encarsia* spp. as biological control agents for whiteflies and is recommended for use in integrated pest management programs.
- The application of fungicides is not compatible with NoFly WP. A week is the minimum period allowed between treatment with fungicides and application of the product. Applications of any other pesticides must be carefully studied, taking into account that the active substance of NoFly WP consists of a microorganism and any substance that could affect its viability must be avoided.

1.4 Mode of Action

NoFly WP contains blastospores of the entomopathogenic fungus *Paecilomyces fumosoroseus* strain FE 9901, which adhere to insect cuticle and germinate rapidly. This fungus can infect all life stages of whiteflies, penetrating the cuticle and growing within the insect, leading to mortality in 3-7 days.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganism

Growth of *P. fumosoroseus* on potato dextrose agar is floccose with a circular margin. Colonies are white, often turning pale yellow from the margin out and changing to brownish-gray when forming conidia. Conidial structures consist of single phialides or in whorls occurring irregularly along aerial hypha. Colony morphology differs from that of *Penicillium* sp. by not producing bright green or blue-green colonies. Molecular fingerprints of *P. fumosoroseus* strain FE 9901 were compared with those of three other isolates of *P. fumosoroseus* by the Molecular Biology

Laboratory of the CABI Bioscience Institute. Two techniques were used, a) Variable Number Tandom Repeat, also called arbitrarily primer Polymerase Chain Reaction (PCR) finger printing, and b) Inter Simple Sequence Repeat. Other technologies available to identify and characterize the microbe include rDNA Internal Transcribed Spacer sequencing and Random Amplification of Polymorphic DNA-PCR for tracking fate.

2.2 Methods for Establishment of Purity of Seed Stock

Portions of freeze-dried first culture from the original isolate (mother stock) are maintained and preserved by cryopreservation. At regular intervals, mother stock is tested to verify pathogenicity against whitefly under laboratory conditions by applying dilutions to a number of different immature stages and adults of whitefly. If potency is found to be reduced, mother stock is replenished from culture collection. *Paecilomyces fumosoroseus* strain FE 9901 is deposited at the United States Department of Agriculture - Agricultural Research Service Collection of Entomopathogenic Fungal Cultures (USDA-ARSEF).

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The guarantee of the NoFly Technical and NoFly WP is based on the number of viable spores per volume of product. The total spore count is determined by means of a hemacytometer. In addition, the germination rate of each batch must be greater or equal to 80%. Potency data were submitted on batches of NoFly product that were not produced at the proposed manufacturing site, however, the data are acceptable and considered representative of product quality expected from the proposed site. Submission of confirmatory potency data on batches of NoFly Technical and NoFly WP produced at the proposed manufacturing site are required as a condition of registration.

2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

Extracts of cultures of *P. fumosoroseus* strain FE 9901 were found to be cytotoxic to HL60 cells (human lymphoblast-like), human lung cancer cells (Hep-2) and Madin Darby canine kidney cells. These extracts were also found to contain three metabolites, beauverolide M and beauverolide I, as well as 2,6-pyridinedicarboxylic acid which is known to have insecticidal activity. Beauverolides M and I, however, have not previously exhibited a bactericidal, fungicidal, insecticidal or any other direct toxic effect in other studies. Given the positive cytotoxicity test results on mammalian cell cultures, it is possible that there are unknown toxic metabolites, produced by *P. fumosoroseus* strain FE 9901, in NoFly Technical and NoFly WP.

NoFly WP is not intended for use on food or feed crops. Therefore, the establishment of a maximum residue limit (MRL) is not required for *P. fumosoroseus* strain FE 9901 and, as a result, no methods to determine and quantify the microbial pest control agent (MPCA) and relevant metabolites are required.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of NoFly Technical and NoFly WP are acceptable. However, the batch analysis data on microbial contamination submitted by the registrant was conducted on NoFly product produced at a different manufacturing site than the one proposed for registration. The technical grade active ingredient (TGAI) and end-use product are required to meet the accepted microbial contamination release standards of the older site prior to release of the product manufactured at the new site. Certificates of analysis, however, will not need to be submitted to PMRA prior to the sale of product in Canada. Production batches that do not satisfy the contaminant release standards are to be discarded.

Confirmatory microbial contaminant analysis data from five batches, each of NoFly Technical and NoFly WP, produced at the proposed site of manufacture are required as a condition of registration.

2.6 Methods to Determine Storage Stability, Shelf-life of the Microorganism

The viability of a comparable NoFly end-use product was evaluated over a 6-month period when the product was stored at 4°C. The submitted data, however, only support a storage period for NoFly WP of three months at 4°C.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

The PMRA conducted a detailed review of the toxicity and infectivity database for *P. fumosoroseus* strain FE 9901, the active ingredient in NoFly Technical and NoFly WP. The database is considered complete, consisting of studies from the published scientific literature, rationales to waive certain test data requirements and laboratory animal (*in vivo*) studies that included various routes of administration (oral, pulmonary, dermal, eye and intraperitoneal injection). The animal studies were mainly carried out in accordance with currently accepted international testing protocols and good laboratory practices. The acute oral toxicity and infectivity and the acute pulmonary toxicity and infectivity studies, however, were considered supplemental and of limited utility because they were conducted using a pure form of the MPCA rather than the TGAI material. Testing of the TGAI is required to assess the health and safety of the form of the microorganism to be formulated for pesticidal purposes. Waiver requests were deemed acceptable to address the remaining data requirements for the TGAI (i.e., acute pulmonary toxicity/infectivity, acute oral toxicity, acute inhalation toxicity, acute dermal toxicity, dermal irritation and eye irritation). Toxicological test data on the end-use product included acute oral, acute dermal and acute inhalation studies as well as acute eye irritation and primary dermal irritation studies conducted on an equivalent formulation to NoFly WP. The scientific quality of the information and data is high, and the database is considered sufficient to characterize the infectivity and toxicity of this pest control agent and product.

In an acute oral toxicity and infectivity study, groups of fasted, young adult (6–7 weeks) Wistar rats (15 rats/sex) were given a single oral dose of the MPCA, *P. fumosoroseus* strain FE 9901 (100%, 1.0×10^9 CFU/g), in 0.05% Tween 80 at a single dose of 10^8 CFU per animal. The animals were then observed for a period of up to 21 days with scheduled sacrifices 24 hours after application and on Days 3, 7, 14 and 21. Another group of rats (four rats/sex) were untreated and served as a negative control. None of the animals died and no gross pathological changes were noted in sacrificed test animals. Significantly lower body weight gains, however, were noted in male rats treated with *P. fumosoroseus* strain FE 9901 compared to control male rats. In this study, *P. fumosoroseus* strain FE 9901 was of low toxicity (oral $LD_{50} > 10^8$ CFU/animal) and was not infective or pathogenic in the rat. This acute oral toxicity and infectivity study is classified as supplemental because the test substance was not the required TGAI but rather the pure form of the MPCA. This substitution of test material is significant since *P. fumosoroseus* strain FE 9901 can produce metabolites that are cytotoxic to HL60 cells (human lymphoblast-like), human lung cancer cells (Hep-2) and Madin Darby canine kidney cells. The pure form of the MPCA likely contains lower levels of the cytotoxic metabolites than the TGAI and therefore cannot be considered toxicologically equivalent to the TGAI.

In an acute pulmonary toxicity and infectivity study, groups of young adult ferrets (14/sex) were exposed by the intranasal route to MPCA, *P. fumosoroseus* strain FE 9901 (100%, 1.0×10^9 CFU/g), in 0.05% Tween 80 at a nominal dose of 1×10^8 CFU (in 0.5 mL) per animal. Animals were then observed for up to 21 days. Another group of ferrets (4 ferrets/sex) were untreated and served as a negative control. None of the animals died or showed any symptoms of intoxication following treatment. Some animals lost weight during the first week of the study and it is not known if these effects were reversed by the end of the study since this information was not included in the study report. No gross pathological changes were noted. Microbiological examination of lungs, other prescribed organs and body fluids demonstrated minimal persistence and no infectivity of the MPCA. In this study, *P. fumosoroseus* strain FE 9901 was of slight toxicity (pulmonary $LD_{50} > 0.9\times10^8$ CFU/animal) and was not infective or pathogenic in the ferret. Although the study was not conducted on the rat which is the preferred species for acute pulmonary toxicity and infectivity testing, the applicant provided an acceptable rationale for testing the MPCA on the ferret. This acute pulmonary toxicity and infectivity study is classified as supplemental because the test substance was not the required TGAI but rather the pure form of the MPCA. As noted above, this substitution may have affected the outcome of the study.

In an acute intraperitoneal infectivity study, a group of young adult Wistar rats (three/sex) were injected with the MPCA, *P. fumosoroseus* strain FE 9901 (100%, 1.0×10^9 CFU/g), in 0.05% Tween 80 at a dose of 10^7 CFU per animal. Animals were then observed for up to 21 days. Another group of rats (four rats/sex) were untreated and served as a negative control. None of the animals died or showed any symptoms of infectivity after treatment. The test substance had no negative effect upon the body weight and no gross pathological changes were noted. Blood samples were collected during necropsy to evaluate clearance of the MPCA. Based on the study results, *P. fumosoroseus* strain FE 9901 is not considered infective or pathogenic in the rat via the intraperitoneal route of exposure.

In an acute oral toxicity study with a NoFly end-use formulation (Futureco NoFly), containing 2×10^9 colony forming units of *Paecilomyces fumosoroseus* strain FE 9901 per gram, was administered to three female Sprague-Dawley rats as a gavage dose of 5000 mg/kg bw following the up and down procedure. The study was terminated following the stopping rules for this procedure. Each animal was then observed for a period of up to 14 days. None of the animals died or showed any symptoms of intoxication following treatment. There were no body weight effects or gross pathological changes noted in treated animals. In this study, Futureco NoFly was of low toxicity (oral $LD_{50} > 5000$ mg/kg bw) to the rat. This acute oral study is classified acceptable and satisfies the guideline requirement for an acute oral study in the rat.

In an acute inhalation toxicity study, a group of 10-week old Sprague-Dawley rats (five/sex) were exposed by the inhalation route to an undiluted end-use formulation (Futureco NoFly), containing 2×10^9 colony forming units of *Paecilomyces fumosoroseus* strain FE 9901 per gram, for four hours to nose only at a concentration of 2.18 mg/L. Animals were then observed for 14 days. There were no mortalities noted throughout the study. Clinical observations included piloerection and decreased activity which was resolved by day three. All test animals gained body weight throughout the study period and no abnormalities were observed at gross necropsy. In this study, Futureco NoFly was of low toxicity (inhalation $LC_{50} > 2.18$ mg/L) in the rat. This acute inhalation study is classified as acceptable and satisfies the guideline requirement for an acute inhalation study in the rat.

In an acute dermal toxicity study, a group of seven week-old Sprague-Dawley rats (five/sex) was dermally exposed to the end-use product Futureco NoFly, containing 2×10^9 colony forming units of *Paecilomyces fumosoroseus* strain FE 9901 per gram, at a limit dose of 5050 mg/kg bw for 24 hours to an area of not less than 10% of the total body surface. Following exposure, the animals were observed for a period of 14 days. There were no mortalities and all the test animals appeared normal for the duration of the study. All animals gained weight with the exception of one female which failed to gain weight between days seven and 14. At necropsy, two male rats had pale lungs at study termination. In this study, Futureco NoFly was of low toxicity (dermal $LD_{50} > 5050$ mg/kg bw) to the rat and was minimally irritating (i.e., mean irritation score=0.1) following a 24-hour exposure. This acute dermal toxicity study is classified as acceptable and satisfies the guideline requirement for an acute dermal toxicity study in the rat.

In a primary dermal irritation study, adult male New Zealand white rabbits (three) were dermally exposed to 0.5 g of the end-use product Futureco NoFly WP, containing 88% *Paecilomyces fumosoroseus* strain FE 9901 (USDA-ARSEF), in water for 4 hours to an area of skin of approximately 6 cm^2. Animals were then observed for 72 hours and irritation was scored by the method of Draize. Very slight erythema was noted in two test animals one hour after patch removal. All test animals were free of irritation at the 24-, 48- and 72-hour observation timepoints. Based on the calculated maximum irritation score and an irritation index of 0.7/8 (one hour) and 0.17 (respectively), Futureco NoFly WP was slightly irritating to the skin of male New Zealand white rabbits. This dermal irritation study is classified as acceptable and satisfies the guideline requirement for a primary dermal irritation study in the rabbit.

In a primary eye irritation study, 0.1 g of the end-use product Futureco NoFly WP, containing 88% *Paecilomyces fumosoroseus* strain FE 9901, was instilled into the conjunctival sac of the left eye of three adult male New Zealand white rabbits. The treated eyes were not washed following application. The untreated right eye of each test animal served as a negative control. Test animals then were observed for 72 hours and irritation was scored by the method of Draize. After one hour, some redness (grade 1) was observed in one rabbit, and slight to moderate increases in excretion discharge were noted in three rabbits. All test animals were free of irritation at the 24-, 48- and 72-hour observation timepoints. In this study, Futureco NoFly WP was slightly irritating to the eyes of New Zealand white rabbits. This eye irritation study is classified as acceptable and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

In a skin sensitization study with the end-use product, Futureco NoFly WP (containing 88% *Paecilomyces fumosoroseus* strain FE 9901), Dunkin Hartley guinea pigs (10 females) were tested using the method of Magnusson and Kligman. Guinea pigs were subjected to a two-stage induction procedure; a 1% intradermal injection and a 25% topical application. Two weeks following the last induction exposure, a challenge dose was applied as a 25% topical application. Five additional female guinea pigs were exposed to the vehicle during induction then challenged with the test material (negative control). The dermal reactions observed in test animals (left flank) following challenge included confluent, intense erythema and swelling. No visible dermal reactions were observed to the vehicles (right flank) or control animals. In this study, Futureco NoFly WP was a sensitizer in guinea pigs following the Magnusson and Kilgman procedure. This study is classified as acceptable and satisfies the guideline requirement for a dermal sensitization study in the guinea pig.

In an *in vitro* mutagenicity assay, auxotrophic strains of *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* (WP2 uvrA) were exposed to the end-use product, Futureco NoFly WP, in dimethylsulfoxide at concentrations of 5000, 2500, 1250, 625, 312.5 and 156.25 µg/plate in the presence and absence of mammalian metabolic activation (standard plate and pre-incubation methods). No inhibitory cytotoxic effects were noted up to the limit concentration of 5000 µg/plate. The background lawn developed normally and the number of spontaneous revertants was normal in all tested strains with and without S9 activation. The positive controls induced the appropriate responses in the corresponding strains. In this reverse gene mutation assay, Futureco NoFly WP was not a mutagen in the tested strains of *S. typhimurium* and *E. coli* under the conditions of the study. This study is classified as acceptable.

Paecilomyces fumosoroseus is a naturally occurring fungus in most countries and occurs in various soil types at very low densities. Strain FE 9901 is intended to control all stages of whitefly (eggs, all stages of larvae and adults), but this species can infect a wide range of insect species. A search in the database of PubMed (http://ncbi.nlm.nih.gov/pubmed) and ToxNet (http://toxnet.nlm.nih.gov) using the keywords "paecilomyces fumosoroseus" or "isaria fumosorosea" found no reports of adverse effects, but other *Paecilomyces* species have been implicated in infections. *Paecilomyces lilacinus* is known to infect the cornea of the eye in humans causing keratomycosis. This species, however, was demonstrated to belong in a different taxonomic clade. Other species have been shown to be opportunistically pathogenic to humans. *Paecilomyces variotii, P. puntonii, P. marquandii, P. javanicus* and *P. lilacinus* have been

reported to cause rare instances of opportunistic infections such as peritonitis, hyalohyphomycosis, cutaneous infections, sepsis, endophthalmitis, cellulitis, fungemia, endocarditis and hypersensitivity pneumonitis. *Paecilomyces fumosoroseus* strain FE 9901, however, does not grow above 35°C and is unable to resume growth after incubation at 37°C.

As previously noted, the MPCA, *P. fumosoroseus* strain FE 9901, produces three known metabolites, i.e., 2,6-pyridinedicarboxylic acid, and beauverolides M and I and may produce unknown cytotoxic substances (metabolites). In *in vitro* studies, cell culture extracts were shown to be cytotoxic to human lung cancer cells and Madin Darby canine kidney cells. Concentrations of these cytotoxic metabolites in NoFly Technical and NoFly WP are unknown. Furthermore, the toxicological activity of these metabolites in animals is also unknown. Acute oral toxicity and infectivity testing on the pure form of the MPCA did not produce any adverse effect; however, the MPCA test material likely contains lower concentrations of these metabolites than the TGAI. Although an acute oral toxicity study was conducted on the Futureco NoFly end-use product, which showed no toxicological effects, only three female animals were tested and, therefore, was not considered to be an acceptable substitute for a full guideline toxicity/infectivity study on the TGAI.

Higher tier subchronic and chronic toxicity studies were not required because of the low acute toxicity of the test substance and no indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute toxicity/infectivity tests. Additional data on the presence of cytotoxic metabolites in the TGAI and end-use product, however, will be required if applications to food or feed crops are pursued by the registrant.

Within the available scientific literature, there are no reports that suggest *P. fumosoroseus* strain FE 9901 has the potential to cause adverse effects on the endocrine system of animals. The submitted toxicity/infectivity studies in the rodent and ferret indicate that, following oral, pulmonary and injection routes of exposure, the immune system is still intact and able to process and clear the blastospores of *P. fumosoroseus* strain FE 9901. Based on the weight of evidence of available data, no adverse effects to the endocrine or immune systems are anticipated for *P. fumosoroseus* strain FE 9901.

The toxicity and infectivity data are summarized in Appendix 1, Table 1.

3.2 Occupational / Bystander Exposure and Risk Assessment

3.2.1 Occupational

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary source of exposure to workers being dermal. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed.

Paecilomyces fumosoroseus has not been identified as a pathogen, and there is no indication that it could infect healthy individuals. While submitted toxicity data on *P. fumososroseus* strain FE 9901 are equivocal, it demonstrated no infectivity in toxicity/infectivity studies and minimal irritation in dermal and eye irritation studies.

Although the overall risk to individuals exposed to large quantities of *P. fumosoroseus* strain FE 9901 is low, hypersensitivity reactions could develop upon repeated exposure to products containing this MPCA. The PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, and furthermore an end-use product containing *P. fumosoroseus* strain FE 9901 was determined to be a sensitizer in a dermal sensitization study in guinea pigs. Consequently, the signal words "Potential Sensitizer" and additional statements describing appropriate risk mitigation measures aimed at minimizing occupational exposures are required on the NoFly WP label. Applicators and handlers are required to wear personal protective equipment, including waterproof gloves, long-sleeved shirts, long pants, NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), shoes and socks. Workers are restricted from entering treated areas during the restricted entry interval of four hours unless they wear long-sleeved shirt, long pants, shoes plus socks and waterproof gloves. Early-entry workers are also required to wear a NIOSH approved respirator with any N-95, R-95, P-95 or HE filter for biological products until spray mists have settled. Applicators, mixer/loaders, handlers and early-entry workers are not required to wear eye goggles since minimal eye irritation was observed in the eye irritation study.

3.2.2 Bystander

Inhalation or dermal exposure to the general public is expected to be low based on the proposed use of NoFly WP in greenhouses only. Overall, it is not expected that bystander exposures will pose an undue risk on the basis of the low toxicity/infectivity profile for *P. fumosoroseus* strain FE 9901 and the associated end-use product, NoFly WP.

The label does not allow applications to turf, residential or recreational areas; therefore, non-occupational dermal exposure and risk to adults, infants and children are low. Because the use sites are in greenhouses, exposure to infants and children in school, residential and daycare facilities is likely to be minimal to non-existent. Consequently, the health risk to infants and children is expected to be negligible.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

As there are no direct applications to food, there is no concern for risks posed by dietary exposure of the general population, including infants and children, or animals. Consequently, the establishment of an MRL is not required for *P. fumosoroseus* strain FE 9901. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent.

3.3.2 Drinking Water

The likelihood that *P. fumosoroseus* strain FE 9901 could enter neighbouring aquatic environments as a result of the greenhouse use of NoFly WP is negligible. No risks are expected from exposure to this microorganism via drinking water because exposure will be minimal and because there were few harmful effects observed in Tier I acute oral toxicity and infectivity testing. Furthermore, the NoFly WP label instructs users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Users are also prohibited from allowing effluent or runoff from greenhouse facilities containing this product to enter lakes, streams, ponds or other waters. Furthermore, municipal treatment of drinking water is expected to remove the transfer of residues to drinking water. Therefore, potential exposure to *P. fumosoroseus* strain FE 9901 in surface and drinking water is negligible.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

As the end-use product, NoFly WP, is not approved for direct applications to food crops, dietary risks to sensitive subpopulations is not expected for *P. fumosoroseus* strain FE 9901.

3.4 Maximum Residue Limits

As there are no direct applications of NoFly WP to food crops, the establishment of a maximum residue limit was not required for *P. fumosoroseus* strain FE 9901.

3.5 Aggregate Exposure

As dietary (food and drinking water) exposures and non-occupational exposures (dermal and inhalation) are expected to be minimal to non-existent, an aggregate exposure assessment was not conducted for *P. fumosoroseus* strain FE 9901.

3.6 Cumulative Effects

The PMRA has considered available information on the cumulative effects of such residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children of such residues and other substances with a common mechanism of toxicity. Besides naturally occurring strains of *P. fumosoroseus* in the environment, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with this active ingredient. No cumulative effects are anticipated if the residues of *P. fumosoroseus* strain FE 9901 interact with related strains of this microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate testing is intended to demonstrate whether a MPCA is capable of surviving or replicating in the environment to which it is applied, and could provide an indication of which non-target organisms may be exposed to the MPCA as well as provide an indication of the extent of exposure. Environmental fate data are not normally required for Tier I risk assessment purposes and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing. Since no significant toxicological effects are expected from the greenhouse use of NoFly WP, no fate data are required to complete the environmental risk assessment of NoFly Technical and NoFly WP.

4.2 Environmental Risk Characterization

4.2.1 Risks to Terrestrial Organisms

Two studies were submitted to address the hazards of *P. fumosoroseus* strain FE 9901 to terrestrial arthropods.

In one study, six laboratory assays were conducted on two non-target parasitic hymenopterans (*Encarsia formosa* and *Eretmocerus mundus*) and two non-target predatory heteropterans (whitefly enemies - *Macrolophus caliginosus* and *Orius laevigatus*) as well as a short-term test on *O. laevigatus* under semi-field conditions. In the laboratory assays, adult or nymph stages of the non-target arthropods were exposed by contact routes to leaf discs from plants treated until run-off with Futureco NoFly (target rate: 1×10^5 CFU/cm^2 leaf) or conventional chemical insecticide controls: Cypermethrin 10% (guarantee 10% cypermethrin), Deltamethrin 2.5 EC (guarantee 2.5% deltamethrin), or Atominal 10 EC (guarantee 100 g pyriproxyfen/L). In the semi-field test, nymphs of *O. laevigatus* were similarly exposed to leaves of tomato plants that were manually sprayed to run-off with Futureco NoFly (target rate: 5×10^4 CFU/cm^2 leaf) or conventional chemical insecticide controls (Deltamethrin 2.5 EC, or Atominal 10 EC). Prior to the addition of the non-target insects, treated plants were covered with eggs of *Ephestia kuehniella* and pollen as food sources. These tests were not consistent with standard test guidelines such as the Office of Chemical Safety and Pollution Prevention (OCSPP) Guideline 885.434, however, the methods were scientifically valid and thus useful for evaluating short-term exposures of the MPCA, *P. fumosoroseus* strain FE 9901, to non-target hymenopterans and heteropterans. In these tests, *P. fumosoroseus* strain FE 9901 was toxic and/or infectious to the predatory heteropterans, *M. caliginosus* and *O. laevigatus*.

In the second non-target terrestrial arthropod study, honeybees (*Apis mellifera*) were tested by oral and contact routes to sugar solutions containing different concentrations of Futureco NoFly (containing *P. fumosoroseus* strain FE 9901, 18% w/w). The tests included a 50% sugar solution negative control and a chlorpyrifos positive reference control group. The study author argued that the tests were scientifically valid because: a) <15% mortality was noted during the first 72 hours in the sugar solution control group; (b) there was no bee mortality noted in the treatment group within the first 72 hours of exposure; and (c) there was 100% bee mortality

observed in the chlorpyrifos reference group after 24 hours of exposure. The two tests were conducted in accordance with International Organisation of Biological Control (IOBC) guidelines, but were not consistent with standard OECD or U.S.A. EPA test guidelines. Notably there were high mortalities in the untreated controls in each study (≥ 20% after 72 hours) which according to OECD and U.S.A. EPA test guideline criteria invalidates the test results. Furthermore, because testing was of insufficient duration and test animals (bees) were of variable or unknown age, the study is of limited value for regulatory risk assessment purposes. Consequently, the potential for *P. fumosoroseus* strain FE 9901 to harm bees remains unknown.

In addition to the above non-target terrestrial arthropod studies, a scientific rationale was submitted to waive testing on birds, mammals, arthropods, non-arthropod invertebrates, microorganisms and plants based on the properties of the MPCA, and the limited potential for exposure from the proposed use of NoFly WP in greenhouses.

Paecilomyces fumosoroseus is a naturally occurring fungus in most countries and occurs in various soil types at very low densities. The fungus is an entomopathogen and has frequently been isolated from lepidopteran cadavers in Europe, including the Netherlands, Ireland and Spain. The fungus has also been found in various non-European countries such as China, Japan, Ghana, Pakistan, India and the United States. In its natural environment, *P. fumosoroseus* is dispersed as conidia or blastospores, either by air or water movement, or by other insects and/or mites. The mode of infection of this species is similar to other entomopathogenic fungi where a typical infection cycle proceeds as such: conidial attachment, germination, penetration, vegetative growth, and then conidiogenesis.

Paecilomyces fumosoroseus strain FE 9901 was first isolated from an adult of *Bemisia tabaci* in Padappai, India in 1992 and was deposited at the United States Department of Agriculture-Agricultural Research Service Collection of Entomopathogenic Fungal Cultures (USDA-ARSEF) under the accession number ARSEF 4490. It remains a wild type strain and is neither a spontaneous nor an induced mutant of the original isolate.

The infection cycle of *P. fumosoroseus* strain FE 9901in the whitefly is particularly rapid under optimal environmental conditions. Initially, conidia are attached to the cuticle or the dorsum of immature or adult whiteflies. The first symptoms of infection typically are apparent within one to two days after contact. Conidia and hyphae are present in the host hemocoel within one day. Fungal multiplication takes place through formation of hyphal bodies or blastospores. The mycelium is present on the dorsum of the insect body within two days. Sporulation occurs within three days and reaches a maximum within five to seven days. Conidiospores generated from the mycelial growth on dead insects can infect additional live target pests. *Paecilomyces fumosoroseus* strain FE 9901 is also unique amongst entomopathogenic fungi in that it can also infect whitefly eggs. In laboratory studies, *P. fumosoroseus* strain FE 9901 produced infections in the N1 and N4 nymph stages of development and significantly reduced the hatching capacity of eggs of *Lecanoides floccissimus*.

It also produced infections in *Aleurodicus disperses* N1 and N4 nymph stages and reduced the hatching of eggs by 50%. Moreover, under certain culture conditions in the laboratory, *P. fumorsoroseus* strain FE 9901 has been shown to produce 2,6-pyridinedicarboxylic acid, a metabolite that is toxic to some insect species.

Minimal exposure to birds, wild mammals and plants is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouse ornamentals. Terrestrial insects and other non-arthropod invertebrates may be exposed to *P. fumosoroseus* strain FE 9901 through contact with treated plant matter, and to a lesser extent, other animals that feed on them. A search in the databases of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), TOXNET (http://toxnet.nlm.nih.gov/), and AGRIS (http://agris.fao.org/) using the keywords "paecilomyces fumosoroseus", "isaria fumosorosea", "monilia aquatilis", "paecilomyces hibernicus", "paecilomyces isarioides", "spicaria aphodii", and "spicaria fumosorosea" yielded numerous reports of biological control attempts against various insect pest species, including silverleaf whitefly (*Bemisia argentifolii*), whitefly (*Bemisia tabaci*), mediterranean fruit fly (*Ceratitis capitata*), cabbage maggot (*Delia radicum*), greenhouse whitefly (*Trialeurodes vaporariorum*), small green leafhoppers (*Empoasca* spp.), horn fly larvae (*Haematobia irritans*), asian citrus psyllid (*Diaphorina citri*), horse chestnut leaf miner (*Cameraria ohridella*), oriental leafworm moth (*Spodoptera litura*), aphids (*Aphis gossypii*, *Myzus persicae*, *Diuraphis noxia*, *Monellia caryella*, *Melanocallis caryaefoliae*, *Brevicoryne brassicae* and *Monelliopsis pecanis*), diamondback moth (*Plutella xylostella*), fall armyworm (*Spodoptera frugiperda*), mosquito (*Aedes aegypti*), corn delphacid (*Peregrinus maidis*, planthopper (*Delphacodes kuscheli*), corn leafhopper (*Dalbulus maidis*), cabbage moth (*Mamestra brassicae*), and cotton leafworm (*Spodoptera littoralis*), corn rootworm (*Diabrotica speciosa*), termite (*Coptotermes curvignathus*), Triatomid bug (*Rhodnius prolixus*), leucaena psyllid (*Heteropsylla cubana*), pine gall midge (*Thecodiplosis japonensis*), small white butterfly (*Pieris rapae*), thrip (*Thrips palmi*), higher termite (*Macrotermes subhyalinus*), peach fruit moth (*Carposina niponensis*), and pear psylla (*Cacopsylla pyricola*), as well as other pests such as root rot nematodes (*Meloidogyne javanica*, *Meloidogyne incognita*), broad mites (*Polyphagotarsonemus latus*), southern cattle tick (*Rhipicephalus microplus*), two-spotted spider mite (*Tetranychus urticae*), cucumber powdery mildew (*Sphaerotheca fuliginea*), brown dog tick (*Rhipicephalus sanguineus*), and sugarbeet nematode (*Heterodera schachtii*). This literature search also yielded reports of adverse effects to beneficial arthropods such as the hymenopteran, *Aphelinus asychis*, and the lady beetle, *Hippodamia convergens*. No adverse effects to birds, wild mammals, and plants were found. Furthermore, the survival of conidia or mycelia ingested via feed or direct colonization of birds and mammals is unlikely because no growth was observed in *P. fumosoroseus* strain FE 9901 at temperatures greater than or equal to 35°C. Acute mammalian toxicity and pathogenicity testing with *P. fumosoroseus* strain FE 9901 produced minimal effects (see Section 3.1). Spores of *P. fumosoroseus* strain FE 9901 were not pathogenic or infective in the rat via the oral and intraperitoneal injection exposure routes and were not pathogenic or infective to the ferret via the pulmonary exposure route. The end-use product, Futureco NoFly, was of low toxicity to rat via the oral, inhalation and dermal exposure routes, and was slightly irritating to the skin and eyes of rabbits. Futureco NoFly, was also a sensitizer to guinea pigs, but was not a mutagen in the bacterial systems.

Based on all the available data and information on the effects of *P. fumosoroseus* strain FE 9901 to non-target organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, plants and other microorganisms from the proposed use of NoFly WP. Test data on the bee were equivocal and no conclusion about the risk of *P. fumosoroseus* strain FE 9901 could be reached. Although *P. fumosoroseus* is a broad-spectrum bioinsecticide that could potentially adversely affect bees present in greenhouses, there are no reports in the open scientific literature to suggest *P. fumosoroseus* is pathogenic or toxic to bees. Honeybees are rarely used for pollination in commercial greenhouses, and even if honeybees were exposed to *P. fumosoroseus* strain FE 9901 through indirect exposure, the environmental conditions in hives are not conducive to the growth of this MPCA. Bumble bees, the pollinators most often used in greenhouses for pollination, are purchased from various commercial sources and possess a limited lifetime of 10 to 12 weeks. The queens and/or hives from these greenhouses are never returned to their commercial sources for fear of pesticide exposure and/or parasites. Furthermore, these colonies contain far more bees than are necessary for pollinating plants in greenhouses and can therefore suffer mortalities without any ill effect to their role in pollination. The potential effects to non-target pollinators and beneficial insects should be limited to the treated areas and the immediate surroundings around treated plants. Because the spores of *P. fumosoroseus* strain FE 9901 are sensitive to heat and ultraviolet radiation, they are expected to be short-lived in greenhouse environments. Levels of this MPCA are therefore expected to quickly decline following greenhouse applications especially during daylight hours when temperatures are at their highest. However, due to the potential for adverse effects on beneficial arthropods and pollinators in treated greenhouses, precautionary measures are required on the NoFly WP label to alert operators of the potential hazard to beneficial insects that may be used in greenhouse integrated pest management programs. Users are also to be advised to avoid direct applications to bees while they are foraging (if employed in the greenhouse).

The toxicity data for non-target species is summarized in Appendix 1, Table 2.

4.2.2 Risks to Aquatic Organisms

No studies were submitted to address the hazards of *P. fumosoroseus* strain FE 9901 to non-target aquatic organisms. Instead, a scientific rationale was submitted to waive testing on fish, aquatic arthropods, aquatic non-arthropod invertebrates and aquatic plants. This rationale was also based on the properties of the MPCA, and the limited potential for exposure from the use of NoFly WP in greenhouses.

No reports of adverse effects on aquatic organisms were found in the published scientific literature following a search in the databases of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), TOXNET (http://toxnet.nlm.nih.gov/), and AGRIS (http://agris.fao.org/) using the keywords "paecilomyces fumosoroseus", "isaria fumosorosea", "monilia aquatilis", "paecilomyces hibernicus", "paecilomyces isarioides", "spicaria aphodii", and "spicaria fumosorosea". The ability of *P. fumosoroseus* to grow and establish itself in water is not known, however, this species is not generally considered a water-borne fungus. As noted in section 4.2.1, negligible environmental exposure, including exposure to aquatic habitats, are expected from the use of NoFly WP in greenhouses.

Based on the absence of available data on the effects of *P. fumosoroseus* to aquatic organisms, there is reasonable certainty that no harm will be caused to non-target aquatic organisms from the use of NoFly WP. As a precaution, standard label statements will prohibit handlers from contaminating aquatic habitats during application, clean-up and repair, as well as prohibit the effluent and run-off of treated greenhouses from entering lakes, streams, ponds or other waters.

5.0 Value

5.1 Effectiveness Against Pests

Efficacy data were submitted from four laboratory studies and three greenhouse trials conducted in Spain between 2002 and 2004. Laboratory studies, mostly on leaf disks in Petri dishes, produced very high levels of mortality (100% in most cases) in larvae and pupae representing four different species of whitefly, including the two most important pest species for greenhouse crops (the greenhouse whitefly, *Trialeurodes vaporariorum*, and the sweetpotato whitefly, *Bemisia tabaci*). Greenhouse trials on mature tomato plants yielded lower levels of mortality but reduced whitefly populations significantly compared to the untreated controls and to an extent that was not significantly different from treatment with commercial standard products containing the active ingredient pyriproxyfen.

5.1.1 Acceptable Efficacy Claims

The submitted efficacy data support a general claim of control of whiteflies on ornamental crops grown in greenhouses when NoFly WP is applied at the rate of 3 g/L as a foliar spray with sufficient volume to provide thorough coverage, up to a maximum of 2000 L/ha.

5.2 Phytotoxicity to Host Plants

No trials were conducted specifically to test for phytotoxicity; however, in two of the three greenhouse efficacy trials it was noted that no signs of phytotoxicity were observed in any of the treated host plants. Furthermore, *P. fumosoroseus* is thought to be incapable of infecting plant tissues.

5.3 Economics

No economic analysis was conducted for this product evaluation.

5.4 Sustainability

5.4.1 Survey of Alternatives

Numerous commercial class pest control products, representing several different insecticide mode-of-action groups, are currently registered for use against whiteflies in greenhouse ornamentals (Appendix 1, Table 3). Many of those products are registered for use against greenhouse whitefly only, although a few are registered for use against additional species of whiteflies and some have general "whitefly" or "whiteflies" label claims. Also, many of those products are registered for use on only one crop or very few crops within the general crop group.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

NoFly WP is generally compatible with current management practices for greenhouse-grown crops. NoFly WP has been shown not to adversely affect species of *Encarsia*, parasitoids commonly used as biological control agents for whiteflies in greenhouses. However, *P. fumosoroseus* is known to infect a wide range of insects and has been shown to cause high levels of mortality in certain insect predators. Therefore, compatibility of NoFly WP with other natural enemies of whiteflies requires further investigation. Fungicides should not be applied within one week of the application of NoFly WP. Compatibility of NoFly WP with other pesticides (e.g., insecticides) has not been established.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The development of resistance to entomopathogenic fungi has not been documented and, due to the relatively complex nature of the mode of action, is not considered likely.

5.4.4 Contribution to Risk Reduction and Sustainability

NoFly WP provides an additional alternative to products currently registered for control of whiteflies on ornamental crops grown in greenhouses, many of which are conventional chemicals belonging to older insecticide groups.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives.

One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

While reviewing *Paecilomyces fumosoroseus* strain FE 9901, the PMRA took into account the federal Toxic Substances Management Policy and followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with its use were also considered, including microcontaminants in the technical product, NoFly Technical, and formulants in the end-use product, NoFly WP. The PMRA has reached the following conclusions:

NoFly Technical does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products. There are also no formulants, contaminants or impurities present in the end-use product that would meet the TSMP Track 1 criteria. Therefore, the use of NoFly WP is not expected to result in the entry of Track 1 substances into the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

NoFly Technical does not contain any formulants of health or environmental concern identified in the Canada Gazette, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* (Amended June 25, 2008 SI\2008-67). There are also no formulants or contaminants of health or environmental concern present in the associated end-use product, NoFly WP.

7.0 Summary

7.1 Methods for Analysis of the Micro-organism as Manufactured

The product characterization data for NoFly Technical and NoFly WP were adequate to assess their potential human health and environmental risks. The TGAI was fully characterized and the specifications were supported by surrogate batch analysis data. However, microbial contamination and potency testing are required on NoFly Technical and NoFly WP produced at the proposed manufacturing to ensure they meet the registrant's quality control standards. Furthermore, confirmatory batch analysis data for potency and microbial contamination from five full scale productions lots of NoFly WP and NoFly Technical from the proposed manufacturing site must be submitted to PMRA as a condition of registration. Storage stability data were sufficient to support a shelf life of three months at 4°C.

7.2 Human Health and Safety

The acute toxicity and infectivity studies and other relevant information submitted in support of *P. fumosoroseus* strain FE 9901 were determined to be sufficiently complete to permit a decision on registration. Spores of *P. fumosoroseus* strain FE 9901 were not pathogenic or infective in the rat via the oral and intraperitoneal injection exposure routes and were not pathogenic or infective to the ferret via the pulmonary exposure route. An equivalent end-use product to NoFly WP, Futureco NoFly, was of low toxicity to the rat via the oral, inhalation and dermal exposure routes, and was slightly irritating to the skin and eyes of rabbits. Futureco NoFly was a sensitizer to guinea pigs and was not a mutagen in bacterial assays.

When handled according to prescribed label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary source of exposure to workers being dermal and to a lesser extent inhalation. Precautionary statements on the NoFly WP label and the wearing of personal protective equipment by workers will adequately mitigate the risks from exposure. While *P. fumosoroseus* strain FE 9901 is a sensitizing agent, inhalation and dermal exposure is not a concern if the required dust/mist filtering respirator/mask and appropriate personal protective equipment stipulated on the NoFly WP label are worn by handlers and applicators. Furthermore, precautionary labelling will alert users of the potential sensitization hazard of the product.

The health risk to general population, including infants and children, as a result of bystander exposure and/or chronic dietary exposure is expected to be minimal since NoFly WP will only be applied to greenhouse ornamentals. The product is not to be applied to residential or recreational areas or to food or feed crops.

7.3 Environmental Risk

The non-target studies on beneficial arthropods and bees, scientific rationale and supporting published scientific literature submitted in support of *P. fumosoroseus* strain FE 9901 were determined to be sufficiently complete to permit a decision on registration. The use of NoFly WP containing *P. fumosoroseus* strain FE 9901 is not expected to pose a risk to birds, mammals, aquatic arthropods, fish, plants and other microorganisms, but may pose a risk to certain beneficial insects and pollinators present in treated greenhouses as well as to non-target terrestrial arthropods and non-arthropod invertebrates present on treated greenhouse crops. These effects are expected to be limited to the treated areas and their immediate surroundings.

No additional studies were required to address the environmental fate and behaviour of *P. fumosoroseus* strain FE 9901. Environmental fate data are higher tier requirements and are not normally required in the absence of significant toxicological effects in non-target organisms in Tier I testing. Environmental exposure to *P. fumosoroseus* strain FE 9901 is expected to be minimal given that the use of NoFly WP is limited to greenhouses.

As a general precaution, the NoFly WP label prohibits the direct application of NoFly WP to aquatic habitats (such as lakes, streams and ponds) and the release of greenhouse effluent and run-off to natural aquatic systems. The label also directs users to avoid contaminating surface water by disposal of equipment wash waters.

The product label also advises users that NoFly WP may be harmful to pollinators (including bees) and to some beneficial insects that may be used in greenhouse integrated pest management programs. A statement also instructs users to avoid directly exposing bees while they are foraging.

7.4 Value

NoFly WP has value for control of whiteflies on ornamental crops grown in greenhouses. The acceptability of the proposed label claims are summarized in Appendix 1, Table 4.

7.5 Unsupported Uses

None.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of NoFly Technical and NoFly WP, containing the technical grade active ingredient *Paecilomyces fumosoroseus* strain FE 9901, to control whiteflies in greenhouse crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

Confirmatory analysis data for potency and microbial contamination are required from five full-scale production lots of NoFly WP and NoFly Technical produced at the proposed site of manufacture. The data must be provided to the PMRA within three years of the original registration decision for these products.

List of Abbreviations

♀	female
♂	male
µg	microgram(s)
µm	micrometre(s)
°C	degree(s) Celsius
AGRIS	global public domain database on agricultural science and technology which is maintained by the Food and Agriculture Organization of the United Nations
a.i.	active ingredient
bw	body weight
cc	cubic centimetre(s)
CFU	colony forming unit(s)
cm^2	centimetre(s) squared
DNA	deoxyribonucleic acid
EC	emulsifiable concentrate
FDA	Food and Drugs Act
g	gram(s)
ha	hectare(s)
IOBC	International Organisation of Biological Control
kg	kilogram(s)
L	litre(s)
lbs	pound(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
m^2	square metre(s)
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MPCA	microbial pest control agent
MRL	maximum residue limit
N1	first nymphal stage
N4	fourth nymphal stage
NIOSH	National Institute for Occupational Safety and Health
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Co-operation and Develpoment
oz	ounce(s)
PCR	Polymerase Chain Reaction
PMRA	Pest Management Regulatory Agency
ppm	parts per million
psi	pound(s) per square inch
PubMed	global public domain database on life sciences and biomedical topics which is maintained by the United States National Library of Medicine
rDNA	ribosomal deoxyribonucleic acid
sq ft	square foot/feet
TGAI	technical grade of the active ingredient

TOXNET	Toxicological Data Network – a group of databases on toxicology, hazardous chemicals, and related information which is maintained by the United States National Library of Medicine
TSMP	Toxic Substances Management Policy
	U.S.A. EPA United States of America Environmental Protection Agency
	USDA-ARSEF United States Department of Agriculture - Agricultural Research Service Collection of Entomopathogenic Fungal Cultures
WP	wettable powder
w/w	wet weight per wet weight

Appendix I Tables and Figures

Table 1 Toxicity and Infectivity of *Paecilomyces fumosoroseus* strain FE 9901

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Acute Toxicity/Infectivity of NoFly Technical (TGAI)				
Acute Oral Toxicity and Infectivity	Rat – Sprague Dawley 15/sex dosed with 10^8 CFU *P. fumosoroseus* strain FE 9901 (MPCA) in 0.05% Tween 80; interim sacrifices (3/sex) on Days 1, 3, 7, 14, and 21 4/sex untreated control	$LD_{50} > 10^8$ CFU/animal	- No mortalities or effect on body weight gain, and no clinical signs of treatment-related toxicity, infectivity or pathogenicity. - No significant findings observed at necropsy. - The MPCA could not be recovered from any of the collected samples and tissues (e.g., feces, kidney, brain, liver, lung, spleen, blood, and mesenteric lymph nodes). **LOW TOXICITY, NOT INFECTIVE** **SUPPLEMENTAL**	1760463

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Acute Pulmonary Toxicity and Infectivity	Ferret 14/sex dosed with 0.5 mL *P. fumosoroseus* strain FE 9901 (MPCA; containing 9×10^7 CFU) in 0.05% Tween 80; interim sacrifices after 1 hour, and on Days 3, 10, and 21 4/sex untreated control	$LC_{50} > 9\times10^7$ CFU/animal	- No mortalities, and no clinical signs of treatment-related toxicity, infectivity or pathogenicity. - 3 ♂ and 3 ♀ lost weight by Day 3. In both sexes, 2 test animals were sacrificed on Day 3 as scheduled (interim sacrifices). It is unknown if the remaining male and female gained weight by study termination since body weight data were missing for Days 14 and 21. Both animals failed to gain weight by Day 10. - No treatment-related findings observed at necropsy. - The MPCA could only be recovered from lungs of treated mice at the 1-hour timepoint (average 372 CFU/g wet weight; range 100–670 CFU/g wet weight) **SLIGHT TOXICITY, NOT INFECTIVE** **SUPPLEMENTAL**	1760465
	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and the results of the acute pulmonary toxicity/infectivity in ferrets. There are no reports of adverse effects associated with this organism in the published scientific literature and strain FE 9901 does not grow at 35°C or 37°C and is killed after incubation at 37°C. No pathogenic effects were observed in the acute pulmonary study in ferrets (see above for details). Although *P. fumosoroseus* strain FE 9901 can produce cytotoxic metabolites, no such adverse effects were observed in an inhalation toxicity study with an end-use formulation containing the MPCA. **WAIVER ACCEPTED**			1760489

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Intraperitoneal Injection Infectivity	Rat – Wistar 3/sex dosed with 10^7 *P. fumosoroseus* strain FE 9901 (MPCA) in 0.05% Tween 80 4/sex untreated control	- no observable effects	- No mortalities or effect on body weight gain, and no clinical signs of treatment-related toxicity, infectivity or pathogenicity. - No significant findings observed at necropsy. - The MPCA could not be recovered from blood of sacrificed animals on Day 21. **NOT PATHOGENIC** **ACCEPTABLE**	1760467
Acute Dermal Toxicity	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and its potential to cause infections or produce toxic metabolites. There are no reports of adverse effects associated with this organism in the published scientific literature and *P. fumosoroseus* strain FE 9901 does not grow at 35°C or 37°C and is killed after incubation at 37°C. Although *P. fumosoroseus* strain FE 9901 can produce cytotoxic metabolites, no such adverse effects were observed in a dermal toxicity study with an end-use formulation containing the MPCA. **WAIVER ACCEPTED**			1760489
Dermal Irritation	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and its potential to cause infections. There are no reports of adverse effects associated with this organism in the published scientific literature and *P. fumosoroseus* strain FE 9901 does not grow at 35°C or 37°C and is killed after incubation at 37°C. Although *P. fumosoroseus* strain FE 9901 can produce cytotoxic metabolites, no such adverse effects were observed in a dermal irritation study with an end-use formulation containing the MPCA. **WAIVER ACCEPTED**			1760489
Dermal Sensitization	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and its potential to cause infections or produce sensitization reactions. There are various reports of hypersensitivity effects associated with the genus *Paecilomyces* and *P. fumosoroseus* strain FE 9901 was previously found to be a sensitizer in a dermal sensitization study with an end-use formulation containing the MPCA. Also, PMRA does not require dermal sensitization testing since most microorganisms contain substances that could elicit a positive reaction in test animals. **WAIVER ACCEPTED**			1760489

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Tissue Culture	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901. There are no reports of adverse effects associated with this organism in the published scientific literature. Tissue/cell culture testing is only required for viruses. **WAIVER ACCEPTED**			1760489
Acute Inhalation Toxicity	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and its potential to cause infections or produce toxic metabolites. There are no reports of adverse effects associated with this organism in the published scientific literature and *P. fumosoroseus* strain FE 9901 does not grow at 35°C or 37°C and is killed after incubation at 37°C. Although *P. fumosoroseus* strain FE 9901 can produce cytotoxic metabolites, no such adverse effects were observed in an inhalation toxicity study with an end-use formulation containing the MPCA. **WAIVER ACCEPTED**			1760489
Eye Irritation	A data waiver was requested based on the biological properties of *P. fumosoroseus* strain FE 9901 and its potential to cause infections. There are no reports of adverse effects associated with this organism in the published scientific literature and *P. fumosoroseus* strain FE 9901 does not grow at 35°C or 37°C and is killed after incubation at 37°C. Although *P. fumosoroseus* strain FE 9901 can produce cytotoxic metabolites, no such adverse effects were observed in an eye irritation study with an end-use formulation containing the MPCA. **WAIVER ACCEPTED**			1760489
Acute Toxicity of NoFy WP (end-use product)				
Acute Oral Toxicity	Rat – Sprague-Dawley 3 ♀ dosed with 5000 mg/kg bw Futureco NoFly (containing 2×10^9 CFU/g *P. fumosoroseus* strain FE 9901) following "up and down" method	LD_{50} > 5000 mg/kg bw	- No mortalities or effect on body weight gain, and no clinical signs of treatment-related toxicity. - No significant findings observed at necropsy. **LOW TOXICITY** **ACCEPTABLE**	1760712

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Acute Inhalation Toxicity	Rat – Sprague-Dawley 5/sex exposed to undiluted Futureco NoFly (containing 2×10^9 CFU/g *P. fumosoroseus* strain FE 9901) at a concentration of 2.18 mg/L for 4 hours nose-only	LC_{50} > 2.18 mg/L	- No mortalities or effect on body weight gain. - Clinical observations included piloerection and decreases in activity which resolved by Day 3. - No significant findings observed at necropsy. **LOW TOXICITY** **ACCEPTABLE**	1760714
Acute Dermal Toxicity	Rat – Sprague-Dawley 5/sex exposed to undiluted Futureco NoFly (containing 2×10^9 CFU/g *P. fumosoroseus* strain FE 9901) at a limit dose of 5050 mg/kg bw for 24 hours to an area of not less than 10% of the total body surface	LD_{50} > 5050 mg/kg bw	- No mortalities and no clinical signs of treatment-related toxicity. - One ♀ failed to gain weight between Days 7 and 14. - At necropsy, two ♂ had pale lungs. **LOW TOXICITY** **ACCEPTABLE**	1760713
Dermal Irritation	Rabbit – New Zealand white 3 ♂ were exposed to 0.5 g Futureco NoFly WP (containing 88% *P. fumosoroseus* strain FE 9901) in water for 4 hours to an area of ~6 cm^2; irritation scored by the method of Draize	Maximum Irritation Score (MIS) = 0.7/8 (at 1 hour)	- Very slight erythema was noted in two animals 1 hour after patch removal. - All irritation had cleared 24 hours after patch removal. **SLIGHTLY IRRITATING** **ACCEPTABLE**	1760720

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference
Eye Irritation	Rabbit – New Zealand white 3 ♂ were instilled with 0.1 g Futureco NoFly WP (containing 88% *P. fumosoroseus* strain FE 9901) into the conjunctival sac of the left eye; irritation scored by the method of Draize	Maximum Irritation Score (MIS) = 3.3/110 (at 1 hour)	- 1 hour after instillation, grade 1 redness was observed in one animal and slight to moderate increases in excretion discharged were noted in 3 animals. - All irritation had cleared 24 hours after patch removal. **SLIGHTLY IRRITATING** **ACCEPTABLE**	1760715
Dermal Sensitization (Magnusson and Kligman)	Guinea Pig – Dunkin Hartley 10 ♀ induced and challenged with Futureco NoFly WP (88% *P. fumosoroseus* strain FE 9901) Induction: Week 1 - 1% intradermal injection Week 2 - 25% topical application Challenge: 25% topical application two weeks after last induction treatment 5 ♀ induced and challenged with vehicles	Positive	- Induction 1 (preliminary results): moderate erythema and very slight erythema after 1 hour; well-defined to moderate erythema after 24 hours; very slight erythema after 48 hours; and no visible change to very slight erythema after 72 hours. - Induction 2 (preliminary results): no visible changes. - Challenge: confluent, intense erythema and swelling was noted after 24 and 48 hours (6/10 positive reactions). **SENSITIZER** **ACCEPTABLE**	1760721

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Terrestrial Organisms				
Vertebrates				
Birds	Oral Pulmonary	A waiver request was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. No adverse effects to birds were found in published literature and *P. fumosoroseus* strain FE 9901 does not grow at temperatures above 35°C. Also, minimal exposure to birds is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**		1793586
Wild Mammals	A waiver request was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. No adverse effects to mammals were found in published literature and *P. fumosoroseus* strain FE 9901 does not grow at temperatures above 35°C. In addition, minimal effects were observed in acute mammalian toxicity and infectivity testing (see Section 3.1) and minimal exposure to wild mammals is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586
Invertebrates				
Arthropods				
Terrestrial Arthropods	*Encarsia Formosa*, *Eretmocerus mundus*, *Macrolophus caliginosus*, and *Orius laevigatus* Contact Toxicity	Futureco NoFly containing *P. fumosoroseus* strain FE 9901 Laboratory Assays: - Adults or nymphs were exposed by contact with leaf discs from plants treated until run-off (target rate: 1×10^5 CFU/cm^2 leaf) -Chemical controls treated with Cypermethrin 10%, Deltamethrin 2.5 EC, or Atominal 10 EC - Negative controls treated with sterile municipal water Semi-Field Test: - Nymphs (N1) of *O. laevigatus* were exposed to tomato leaves sprayed to run-off (target rate:	Laboratory Assays: - Adult *E. formosa* were not significantly affected compared to negative controls (0±0% [±standard error] mortality after 9 days and 11.4±4.71% reduction in parasitism) - Adult *E. mundus* were not significantly affected compared to negative controls (16.3±4.27% mortality after 14 days and 41.7±6.09% reduction in parasitism). - Nymphs (N1) of *M. caliginosus* were significantly affected compared to negative controls (75±2.41% mortality after 9 days). - Nymphs (N4) of *M. caliginosus* were significantly affected compared to negative controls (94.4±3.67% mortality after 9 days).	1793584

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		5×10^4 CFU/cm^2 leaf). -Chemical controls were treated with Deltamethrin 2.5 EC, or Atominal 10 EC - Negative controls treated with sterile municipal water	- Nymphs (N1) of *O. laevigatus* were significantly affected compared to negative controls (100±0% mortality after 9 days). - Nymphs (N4) of *O. laevigatus* were significantly affected compared to negative controls (76±8.67% mortality after 9 days). Semi-Field Test: - Nymphs (N1) of *O. laevigatus* were significantly affected compared to negative controls (41.7±3.69% mortality after 8 days).	
			SUPPLEMENTAL	
	Apis mellifera Oral and Contact Exposure	Futureco NoFly containing *P. fumosoroseus* strain FE 9901 Oral Test: - Honeybees were fed a 1:1 water-sugar solution containing 4 g/L Futureco NoFly or 0.72 g a.i./L over a period of 6 hours. - Chemical controls were fed a 1:1 water-sugar solution containing 1.25 g/L Dursban 75 WG or 0.9375 g a.i. (chlorpyrifos)/L. - Negative controls were fed a 1:1 water-sugar solution. Contact Test: - Honeybees were sprayed with a 1:1 water-sugar solution containing 4 g/L Futureco NoFly or 0.72 g	Oral Test: - Each bee was dosed with an average of 3.46×10^{-5} g Futureco NoFly or 6.23×10^{-6} g a.i. - Each chemical control bee was dosed with 5.6×10^{-4} g Dursban 75 WG or 7.5×10^{-5} g chlorpyrifos. - Cumulative mortalities in Futureco NoFly-treated bees were 0%, 3.3%, 60%, 83.3%, 100% after Days 4, 7, 8, 9 and 10, respectively. -Cumulative mortalities in negative controls were 2.5%, 30%, 47.5%, 70%, 75% and 100% after Days 4, 7, 8, 9, 10, and 11, respectively. - Cumulative mortalities in chemical controls were 100% after 24 hours. Contact Test: - Each bee was treated with an average of 4.24×10^{-4} g Futureco NoFly or 7.63×10^{-5} g a.i.	1793585

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
		a.i./L over 2 seconds. - Chemical controls were sprayed a 1:1 water-sugar solution containing 1.25 g/L Dursban 75 WG or 0.9375 g a.i. (chlorpyrifos)/L. - Negative controls were sprayed with a 1:1 water-sugar solution.	- Each chemical control bee was dosed with 5.6×10^{-6} g Dursban 75 WG or 7.5×10^{-6}g chlorpyrifos. - Cumulative mortalities in Futureco NoFly-treated bees were 0% after 72 hours, and 6.67%, 10%, 13.33%, 16.67%, 33.33%, 70%, 83.33%, and 100% after Days 6, 7, 8, 9, 10, 13, 14 and 15, respectively. - Cumulative mortalities in negative controls were 0%, 2.5%, 2.5%, 2.5%, 5%, 57.5%, 77.5%, 80%, and 100% after Days 6, 7, 8, 9, 10, 13, 14, 15 and 16, respectively. - Cumulative mortalities in chemical controls were 100% after 24 hours. **SUPPLEMENTAL**	
	A waiver request was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. Although *P. fumosoroseus* strain FE 9901 is a broad-spectrum entomopathogen, minimal exposure is anticipated to non-target arthropods from the proposed use of NoFly WP to control whiteflies in greenhouse crops. Users, however, are advised to exercise caution if beneficial insects are used as part of an integrated pest management program. **WAIVER ACCEPTED**			1793586
Non-arthropods				
Terrestrial Non-Arthropod Invertebrates	A waiver was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. Although *P. fumosoroseus* strain FE 9901 is a broad-spectrum entomopathogen, minimal exposure is anticipated to non-target arthropods from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586
Plants				
Plants	A waiver was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. *Paecilomyces fumosoroseus* strain FE 9901 is not a plant pathogen and no adverse effects to plants were found in published literature. In addition, minimal exposure to non-target plants is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586

Organism	Exposure	Protocol	Significant Effect, Comments	Reference
Aquatic Organisms				
		Vertebrates		
Fish	A waiver was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. *Paecilomyces fumosoroseus* strain FE 9901 is not a fish pathogen and no adverse effects to fish were found in published literature. In addition, minimal exposure to non-target fish is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586
		Invertebrates		
Aquatic Arthropods and Non-Arthropod Invertebrates	A waiver was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. Although *P. fumosoroseus* strain FE 9901 is a broad-spectrum entomopathogen, no reports of adverse effects to aquatic invertebrates were found in published scientific literature. In addition, minimal exposure is anticipated to non-target invertebrates from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586
		Plants		
Aquatic Plants	A waiver was submitted based on the properties of the MPCA and limited potential for exposure from the proposed use of NoFly WP in greenhouses. *Paecilomyces fumosoroseus* strain FE 9901 is not a plant pathogen and no adverse effects to aquatic plants were found in published literature. In addition, minimal exposure to non-target aquatic plants is anticipated from the proposed use of NoFly WP to control whiteflies in greenhouses. **WAIVER ACCEPTED**			1793586

Table 3 Alternative Insecticides Currently Registered for Whiteflies on Greenhouse Ornamental Crops

Active Ingredient	Insecticide Group
Acephate	1B
Chlorpyrifos	1B
Dichlorvos	1B
Malathion	1B
Naled	1B
Endosulfan	2A
Permethrin	3A
Pyrethrins	3A
Acetamiprid	4A
Imidacloprid	4A
(S)-Kinoprene	7A
Pyriproxyfen	7C
Pymetrozine	9B
Pyridaben	21A
Spiromesifen	23
Potassium salts of fatty acids (soap)	Not classified
Beauveria bassiana Strain GHA	Not applicable

Table 4 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed label claim	Supported use claim
For Greenhouse Use Only	Accepted as proposed.
For use in controlling Whitefly on all greenhouses and nurseries ornamental crops.	For use in controlling whiteflies on all greenhouse ornamental crops.
NoFly WP contains live blastospores of the naturally occurring fungus *Paecilomyces fumosoroseus* strain FE 9901 and food grade inert ingredients. The spores are alive and may be harmed by storage at high temperatures or contact with water for more than 24 hours. NoFly WP can generally be applied using conventional spraying equipment. Use of manual sprayers is highly recommended; with a minimum working pressure of 4 psi. NoFly WP works best in a pest management program designed to keep insect populations below levels which damage crops. Typically, it takes 3-7 days for an infected insect to die and 7-10 days after the first spray to see a reduction in an insect population. Application rates, spray frequency, spray coverage and insect numbers affect the speed at which insect populations are reduced. Frequent scouting for insects in crops is recommended. NoFly WP is most effective when used at the first appearance of insects in the crop, before high insect populations develop.	Accepted as proposed (with the product name amended to "NoFly WP").
NoFly WP may be combined with chemical insecticides for rapid knockdown of damaging insect populations or large numbers of insects moving into crops.	**Not supported:** No data or other information were submitted to support the compatibility of NoFly WP with chemical insecticides.
Crops Ornamental crops for greenhouse use **Application** At any stage of the crop. Applications must be done at the first sign of insect larvae **Doses** 2.25 – 4.5 kg/hectare (2 - 4 lbs/acre) 22 mL – 46 mL/100 m^2 (8-oz – 16 oz/11,000 sq ft) of greenhouse applied at minimum 0.2% (2.18 mL per L /28-oz per 100 gallons)	**Crops** Greenhouse ornamentals **Application Rate** 3 g/L up to a maximum of 2000 L/ha **Application Timing** At any stage of the crop. Applications must begin at the first sign of pest presence.

Proposed label claim	Supported use claim
First applications should be done at the first symptoms of the presence of larvae or eggs on the leaves. Repeat applications 2 – 3 times at 15 days intervals or shorter (5 – 8 days) in the case of heavy infestations	Begin applications at the first sign of pest presence. Reapply at 15-day intervals, or shorter (5-8 days) in the case of heavy infestations, up to a maximum of three applications.
Apply enough quantity of broth for a good coverage on the plants, trying to reach the lower-sides of the leaves. It is recommended to apply 96.30 mL/m^2 (26 gallons / 11,000 sq ft) greenhouse on small crops and up to 37 L/100 m^2 (100 gallons / 11,000 sq ft) on full grown crops	Apply sufficient spray volume for thorough coverage of the crop, depending on the size of the plants, up to a maximum of 2000 L/ha. Ensure spray coverage includes the undersides of the leaves.
Dissolve the content of bags in appropriate volume of water and mix with a stirring device up to get a blue homogeneous suspension. Apply immediately using conventional spraying equipment. A minimum pressure of four psi is recommended for the applications.	Dissolve the content of bags in appropriate volume of water and mix with a stirring device to get a blue homogeneous suspension. Apply immediately using conventional spraying equipment. A minimum pressure of four psi is recommended for the applications.
Applications should be conducted during low solar radiation (late afternoon or early night) when there is high relative humidity inside greenhouse and temperature is below 30°C.	Applications should be conducted during low solar radiation (late afternoon or evening) when there is high relative humidity inside the greenhouse and the temperature is below 30°C.
NoFly WP supports the action of natural predators of whitefly and other pests, therefore, it is highly recommended as a supporting tool in integrated pest management programs or Organic Agriculture.	NoFly WP is compatible with the use of *Encarsia* spp. as biological control agents for whiteflies and is recommended for use in integrated pest management programs.
The application of fungicides is not compatible with NOFLY™. A week is the minimum period allowed between treatment with fungicides and application of the product. Applications of any other pesticides must be carefully studied, taking into account that the active substance of NOFLY™ consists of a microorganism and any substance that could affect its viability must be avoided.	Accepted as proposed (with the product name amended to "NoFly WP").

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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1793578	2004, Characterisation of the microbial pest control agent Paecilomyces fumosoroseus strain FE 9901, DACO: M2.7.1 CBI
1760710	2009, Product Chemistry of NoFly WP, DACO: M2.10.1, M2.10.2, M2.10.3, M2.12, M2.4, M2.7.1, M2.7.2, M2.8, M2.9.1, M2.9.2, M2.9.3 CBI
1760711	2006, Storage and Stability of NoFly WP, DACO: 2.14.14, 3.5.10, M2.11
1890403	Luangsa, J.J., N.L. Hyel-Jones, L. Manoch and R.A. Samson (2005) On the relationships of Paecilomyces sect. Isarioidea species. Mycol. Res. 109(5): 581 — 589. DACO: 2.16
1890400	2010, Nofly Technical and NoFly WP Response to PMRA and EPA Clarifications, DACO: 2.14.13, 2.14.14, 3.5.10, 3.5.13, 3.5.14, 3.5.9, M2.10.2, M2.10.3, M2.4, M2.7.1, M2.7.2, M2.8 CBI
1890401	2010, Mother Stock Production of Paecilomyces fumosoroseus strain FE9901,DACO:2.14.13,2.14.14,3.5.10,3.5.13,3.5.14,3.5.9,M2.10.2, M2.10.3,M2.4,M2.7.1,M2.7.2,M2.8 CBI
1903717	2010, Response to EPA and PMRA Deficiency Letter, DACO: 0.8.1,M2.11 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
1760460	Mier, T., G. Olivares-Redonda, H. Navarro-Barranco, A. Perez-Mejia, M. Lorenzana, A. Perez-Torres and C. Toriello (2005) Acute Oral Intragastric Pathogenicity and Toxicity in Mice of *Paecilomyces fumosoroseus* Isolated from Whiteflies. Antonie van Leeuwenhoek 88:103-111. DACO: M4.2.1, M4.2.2.
1760463	2004. NoFly Technical Acute Oral Toxicity. DACO: 4.2.1, 4.6.1, M4.2.1, M4.2.2, M4.9.

1760465 2004. NoFly technical Acute Pulonary Toxicity/ Pathogenicity. DACO: M4.2.3.

1760467 2004. NoFly Technical Injection / Pathogenicity (Intraperitoneal). DACO: M4.3.2, M4.3.3.

1760469 2009. Response to Tier 1 Microbial Pesticide Data Requirements for NoFly Technical. DACO: 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.6.2, 4.6.3, 4.6.4, 4.6.5, 4.6.6, M4.2.3, M4.4, M4.5.2, M4.6.

1760473 2004. NoFly technical Bacterial Reverse Mutation Assay. DACO: 4.5.4, M4.8.

1760657 Summary Document. DACO: M4.2.1, M4.3.1, M4.5.1.

1890402 2010. Hypersensitivity Incidents. DACO: M4.6.

1903717 2010. Response to EPA and PMRA Deficiency Letter. DACO: M2.11.

1760712 2009. NoFly - Acute Oral Toxicity in Rats. DACO: 4.2.1, 4.6.1, M4.9.

1760713 2009. NoFly Acute Dermal Toxicity in Rats. DACO: 4.2.2, 4.6.2, M4.4.

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1760721 2004. NoFly WP Skin Sensitization. DACO: 4.2.6, 4.6.6.

3.0 Environment

PMRA Document Number	Reference

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1793584 2004. Evaluation of Side Effects of the Microbial Pest Control Product Futureco NoFly. DACO: M9.5.1.

1793585 2007. Laboratory Trials to Test the Side-Effects of the Test Item Futureco NoFly. DACO: M9.5.1.

1793586 2009. Waiver Request. DACO: M9.6.

4.0 Value

PMRA Document Number	Reference
1760686	2003. Efficacy of FuturEco NoFly™ (technical grade and final product), a new biopesticide for the control of whitefly under laboratory conditions. DACO: M10.2.1
1760687	2002. Efficacy of a formulation based on blastospores of the entomopathogenic fungi *Paecilomyces fumosoroseus* strain FE 9901 (ARSEF 4490) for whitefly control under laboratory conditions. DACO: M10.2.1
1760688	2004. Effects of FUTURECO NOFLY™ (*Paecilomyces fumosoroseus* strain FE 9901) on different life stages of the whitefly *Lecanoideus floccisimus* under laboratory conditions. DACO: M10.2.1
1760689	2004. Effects of FUTURECO NOFLY™ (*Paecilomyces fumosoroseus* strain FE 9901) on different life stages of the whitefly *Aleurodicus dispersus* under laboratory conditions. DACO: M10.2.1
1760692	2002. Capacity of control of Whitefly by *Paecilomyces fumosoroseus* strain FE 9901 (ARSEF 4490) in tomato crops under greenhouse conditions. DACO: M10.2.2
1760693	2002. Capacity of whitefly control by *Paecilomyces fumosoroseus* strain FE 9901 (ARSEF 4490) in horticultural crops on greenhouses. DACO: M10.2.2
1760694	2003. Capacity of whitefly control by *Paecilomyces fumosoroseus* strain FE 9901 (ARSEF 4490) in horticultural crops on greenhouses, varying the application dose. DACO: M10.2.2
1760695	2004. Effect of five fungicides on blastospore germination of *Paecilomyces fumosoroseus* strain FE 9901(ARSEF 4490) active ingredient of FuturEco NoFly™. DACO: M10.3.2.1
1793584	2004. Evaluation of side effects of the Microbial Pesticide Control Product FUTURECO NOFLY™ *Paecilomyces fumosoroseus* strain FE 9901) to whitefly natural enemies in the Canary Islands. DACO: M9.5.1